ON THE PRESENCE OF NEUSSER'S PERINUCLEAR BASOPHILIC GRANULES IN THE BLOOD,

AND THEIR RELATION TO THE ELIMINATION OF THE ALLOXURIC BODIES IN THE URINE.

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The observation, originally made by Neusser,[1] that under certain conditions granules may be found in the blood, which manifest a marked affinity for basic dyes and are located in immediate contact with the nuclei of leucocytes, has received comparatively little attention. This is the more surprising in view of Neusser's claim that these granules are essentially found in patients the subjects of the uric-acid diathesis, and may be regarded as pathognomonic of the disease in the widest sense of the term, viz., including gout, lithiasis, muscular rheumatism, nervous asthma, skin affections, gastro-intestinal derangements, diabetes, leucæmia, neuralgia, and neurasthenia. The only exception to this rule was noted in certain tubercular subjects, in which the granules were at times found, and which Neusser believed pursued a more favorable course than those in which the granules were absent.

Kolisch, a pupil of Neusser's, likewise regards these granules as evidence of the uric-acid diathesis.[2] But, while Neusser believes the diathesis in question to be associated with an increased elimination of uric-acid, Kolisch finds the uric acid relatively diminished, but the xanthin-bases actually increased to such an extent that the alloxuric bodies as a whole are eliminated in increased amount.

The text-books on clinical diagnosis which have since appeared make little mention of the subject. v. Jaksch[3] thus merely states that further observations will show to what extent Neusser's basophilic granules are of diagnostic interest. Cabot[4] likewise brings nothing new. The only other observations upon the subject which I have been able to find recorded in the literature come from Futcher and Fisch, in this country.

Futcher's results, however, in no way bear out the correctness of Neusser's view, and he concludes his most valuable report as follows: These observations do not in any way confirm the theory that there is a regular coincidence between an abundance of the granules and an increased excretion of the alloxuric bodies, nor do they favor the view that Neusser's granules occur exclusively in patients with an alloxuric diathesis. Cases occur in which, with numerous granules in the leucocytes, there is a relatively small amount of the alloxuric bodies eliminated in the urine, while, on the other hand, the granules may be almost entirely absent, and the alloxuric bodies be excreted in increased amount. Such directly opposed conditions may occur in different individuals having the same disease. Not infrequently the granules become increased or diminished in the same person without there being a corresponding increase or diminution in the excretion of the alloxuric bodies. In fact, increase in the number of granules may be accompanied by a diminution of the alloxuric bodies, and *vice versa.* From the information obtained one seems justified in concluding that the supposed relationship between the perinuclear basophilic granules and an alloxuric diathesis, as claimed by Kolisch, is purely empirical.[1] Fisch,[2] on the other hand, claims that in the overwhelming majority of all blood specimens examined not a trace of these bodies can be found. He believes that this fact cannot be too strongly accentuated in order to show that they are certainly something abnormal. From the experiments dealing with four persons (and from other scattered observations), he is of opinion that really abundant perinuclear granule-formation corresponds to an increased uric-acid elimination.

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[1] Neusser. Wiener klin. Wochen., 1894, vii. p. 71.

[2] Kolisch. Ibid., 1895, viii. p. 797.

[3] Clinical Diagnosis. Fourth edition.

[4] Clinical Examination of the Blood. Wm. Wood & Co., New York, 1897.

In view of the importance of the subject, and the scarcity of observations thus far recorded, it seemed necessary to repeat the work done already, and, if possible, to account for the widely divergent results obtained.

The questions which naturally suggested themselves for investigation were the following:

1. Are Neusser's granules found in the human blood under strictly normal conditions?

2. In diseased conditions, are these granules confined to the blood of patients suffering from the uric-acid diathesis?

3. Does a constant relation exist between the presence of these granules in the blood and the elimination of uric acid, xanthin-bases, or both?

Incidentally, it seemed of interest to ascertain to what extent an increased elimination of uric acid, as such, and of the alloxuric bodies as a whole, plays a part in the symptomatology of the uric-acid diathesis.

For practical purposes it was not deemed essential to place the persons to be examined in a condition of nitrogenous equilibrium, and, as a general rule, but one examination both of the blood and urine was made. The blood specimens were obtained within the same twenty-four hours as the urine. The uric acid was estimated according to Hopkins' method as modified by Whitney.[3]

One hundred c.c. of urine are treated with 30 grms. of finely-powdered and chemically pure ammonium chloride. The mixture is thoroughly shaken and set aside for from two to three hours, care being taken to stir it from time to time. It is then passed through a small filter with the aid of mild suction, and the precipitate washed two or three times with a saturated solution of ammonium chloride. With a little boiling water the salt is washed from the filter, and decomposed with 10 c.c. of a decinormal solution of hydrochloric acid. The solution is brought to the boiling-point and the excess of hydrochloric acid not used in the decomposition of the ammonium biurate retitrated with a decinormal solution of sodium hydrate, using a half per cent. alcoholic solution of dimethyl-amido-azo-benzol as an indicator. This excess is deducted from the original ten cubic centimetres. The result, multiplied by 0.0168, will indicate the amount of uric acid contained in 100 c.c. of urine.

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[1] Futcher. Bulletin of the Johns Hopkins Hospital, May, 1897.

[2] Fisch. St. Louis Medical Gazette, 1898, vol. i. p. 10.

[3] Whitney. Maryland Medical Journal, 1898, vol. xxxviii. p. 334.

The xanthin-bases were estimated according to the method of Krüger-Wulff, as described in my *Clinical Diagnosis*.[1]

The blood was drawn from the finger, spread between cover-glasses, dried, fixed in absolute alcohol, stained with Neusser's modification of Ehrlich's tri-acid stain, mounted in oil of cedar, and examined with a 1-12 oil immersion lens. The stain was prepared according to Neusser's directions, and contained

Saturated aqueous solution of acid fuchsin . . .	50 c.c.
Saturated aqueous solution of orange G.	70 "
Saturated aqueous solution of methyl-green . . .	80 "
Distilled water	150 "
Absolute alcohol	80 "
Glycerin	20 "

Prepared in this manner the specific granules appear as greenish-black or entirely black little dots, which are irregularly scattered over the surface of the nucleus, as though they had been pressed out from its substance. In size they vary considerably. Specimens are thus encountered in which the granules are as fine as an ordinary neutrophilic granule, while others are much larger, and in some cases droplets may even be seen which nearly cover the entire nucleus. By a massing together of the granules, moreover, curious figures are at times formed, and it is very common to see specimens in which they form a distinct ring or star on the surface of the nucleus. Their number is likewise subject to considerable variation, some nuclei carrying only a single granule, while on others as many as twenty or even more may be counted.

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[1] This method was used by preference in order to permit of a direct comparison of my results with those obtained by Neusser, Kolisch, and Futcher. At the same time I believe, with Malfatti, that the objections made to this method by Huppert, Salkowski, and others are not altogether valid, as the precipitation of other nitrogenous constituents by sodium sulphite and copper sulphate would scarcely affect the results reached, providing that the precipitate has been thoroughly washed. It has, moreover, not been satisfactorily proved, as yet, that the xanthin-bases are completely thrown down by the silver method, and it is not at all improbable that certain xanthins may form insoluble salts with copper, and not with silver.

Contrary to Neusser's experience, I have found these granules most abundant in the polymorphonuclear elements, although they are very nearly as numerous in the small mononuclear forms. The percentage number of the latter showing granules was 86.5; that of the large mononuclear leucocytes, 40.5; of the transition forms and polymorphonuclear elements, 91.5; and of the eosinophilic leucocytes, 39.4. The largest, average, and smallest number counted in these various forms is seen below:

	Largest Number.	Average Number.	Smallest Number.
Small mononuclear leucocytes	25	4.3	0
Large mononuclear leucocytes	8	1.3	0
Transition forms and polymorphonuclear leucocytes	20	6.3	0
Eosinophilic leucocytes	5	1.5	0

In the first series of fifty cases, which Dr. S. P. Latané examined in my laboratory, the granules, present in every leucocyte on the cover-slip, were counted. In the subsequent cases, however, this attempt was abolished, and the granules were either recorded as absent, or present in very small, small, moderate, large, or excessive numbers, a single glance at each leucocyte being sufficient to place it in its proper category.

In order to ascertain whether or not Neusser's granules ever occur in the blood under strictly normal conditions, special precautions were taken in the selection of the subjects for examination. Only such were taken in which a negative family history as regards gout, rheumatism, lithiasis, and neurasthenia could be obtained, and in which the uric-acid coefficient was larger than one to thirty. In every case thus examined, without exception, the specific granules were found, so that the question, Do Neusser's granules occur in the blood under strictly normal conditions? can be definitely answered in the positive. My results are thus in direct accord with those reached by Futcher, who, "in a very large number of cases examined, both in healthy and diseased persons, never failed to find the granules present." So constant, indeed, is the presence of these granules in health that I feel justified in stating that their *absence* in a supposedly healthy individual may be regarded as presumptive evidence of some morbid process.

To determine the second point—*i. e.*, whether or not in diseased conditions Neusser's granules are to be found only in persons the subjects of the uric-acid diathesis—the blood of every patient occurring in my practice during the past winter was examined in this direction. It was thus found that the granules are almost as constantly present in diseased conditions as in health, and that they are not necessarily more abundant in cases of gout, lithiasis, chronic rheumatism, and neurasthenia than in other conditions. My observations are thus again in accord with those of Futcher, who says: I was able to convince myself that the granules were not more marked in the blood of patients suffering from the so-called uratic diathesis than in other diseases, or even in apparently healthy individuals.

During this series of investigations the interesting fact developed, however, that whereas under normal conditions Neusser's granules are constantly met with in the blood, they may at times be absent in disease, or present in such small numbers as to attract attention. The first cases in which this observation was made were patients with malignant disease, and it occurred to me that possibly the absence of Neusser's granules might be important from the stand-point of differential diagnosis. In this belief I was encouraged through similar observations made by Drs. G. W. Johnston and A. Stewart, of Washington, who reported that in eleven cases of malignant disease, including sarcoma of the kidney and neck, carcinoma of the uterus, stomach, rectum, œsophagus, liver, etc., no perinuclear granules were found in ten. They further state that carefully conducted experiments excluded all probable causes of error, and that the diagnosis in each case was verified by operation or the subsequent history and termination. The eleventh case, in which no perinuclear granules were discoverable, was a negress (all the rest were whites). Here a clinical diagnosis of inoperable malignant disease of the uterus was made, but the patient was lost sight of and her fate is unknown.[1]

Continued investigations, however, taught me that, whereas the granules are quite constantly absent in malignant disease, this may also occur under other pathological conditions, and I have recently observed two cases of gastric ulcer and one case of acute gonorrhœa in which the granules were likewise not to be found. Their absence is thus in no way pathognomonic of malignant disease, but the constancy with which they are missed under such conditions appears to me sufficiently important to merit attention and further investigation.

As far as the occurrence of the granules in tubercular subjects goes, I have not been able to verify Neusser's claim, though I admit that my tubercular material is small. But Futcher also says that in tuberculosis he has observed cases with abundant granules and others with few granules, without having noticed any difference in the subsequent course of the disease.

The third series of experiments was undertaken to ascertain whether or not a constant relation exists between the presence of the granules and the elimination of uric acid, xanthin-bases, or both. To this end a systematic examination of both blood and urine was made in fifty cases, many of which presented marked symptoms of the uric-acid diathesis.

A brief record of these cases follows, and the results obtained are tabulated in Table I.

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[1] The National Medical Review 1898, vol. viii. p. 78.

TABLE I.

No.	Amount.	Density.	Reaction.	Albumin.	Sugar.	Uric acid.	Urea.	Xanthins.	Alloxuric bodies.	Small mononuclear leucocytes.			Large mononuclear leucocytes.			Transition forms and polymorphonuclear leucocytes.			Eosinophilic leucocytes.		
										a	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*
	c.c.									pr.ct.			pr.ct.			pr.ct.			pr.ct.		
1	1020	1.015	Acid	Trace	None	0.2785	10.38	0.4806	0.7091	100	11	7	25	2	0.5	100	20	15	100	2	2
2	1200	1.009	"	"	"	0.66	12.0	0.044	0.704	80	12	8	40	2	1	80	15	8	50	3	½
3	830	1.019	"	None	"	0.1817	11.2	0.353	0.5647	100	8	3	32	3	3	100	10	6	50	2	1
4	1160	1.019	Neutral	"	"	0.8189	15.08	0.52	1.8389	69	9	4	0	0	0	66	12	3	0	0	0
5	1140	1.016	Acid	"	"	0.0399	15.96	0.0107	0.6506	100	7	5	20	4	0.5	92	11	4	50	3	1
6	940	1.026	"	"	"	0.2870	20.32	0.418	0.7096	100	9	7	5	3	1	100	15	11	50	2	1
7	1060	1.021	"	"	"	0.4695	23.32	0.602	1.1615	100	13	6	66	5	2	78	10	4	50	1	0.5
8	860	1.027	"	"	"	0.2836	21.50	1.0791	1.3127	100	6	4	57	2	1	100	15	10	...	...	...
9	720	1.027	"	"	"	0.0408	17.28	0.2234	0.8642	60	8	1	25	1	¼	85	6	8	0	0	0
10	1320	1.019	"	Trace	"	1.1623	18.48	0.0884	1.2407	70	4	1	60	1	1	94	8	4	0	0	0
11	1140	1.010	"	"	"	0.9348	18.24	....	....	80	11	5	25	2	½	93	9	7	0	0	0
12	1420	1.022	"	"	"	0.7866	14.2	....	....	100	10	5	80	3	4	80	11	6	0	0	0
13	1230	1.016	"	None	"	0.5166	15.99	0.7083	1.2253	77	12	4	83	2	1	100	12	8	50	3	1
14	1180	1.020	"	"	"	....	......	....	....	60	8	3	50	3	2	82	8	2	0	0	0
15	1100	1.023	"	"	"	1.266	......	....	....	72	8	3	57	4	1	98	7	3	100	2	1
16	860	1.022	"	"	"	1.144	......	....	....	75	5	2	85	5	3	100	9	5	100	2	1
17	870	1.022	"	"	"	0.8744	......	....	....	100	12	4	60	7	0.5	100	12	10	50	1	1
18	1510	1.016	"	1.5 p.m.	"	0.7097	14.78	....	....	80	9	4	42	4	2	80	8	7	50	2	1
19	2476	1.015	Alkaline	None	"	2.070	22.28	....	....	100	8	3	83	3	1	100	14	6	50	3	2
20	1610	1.016	Acid	"	"	1.9787	24.16	....	....	100	8	5	83	6	2	88	8	4	50	1	½
21	950	1.018	"	"	"	0.1486	12.85	0.6661	0.8100	75	8	4	25	3	1	100	10	4	50	1	1
22	1250	1.022	"	Trace	Trace	0.945	25.0	0.0988	1.0483	100	8	3	50	3	1	100	12	6	50	3	1
23	745	1.021	"	"	None	0.7864	17.88	0.2035	0.9410	...	...	...	...	...	...	...	...	...	...	...	...
24	970	1.019	"	None	"	0.4563	14.55	0.4642	0.9205	100	6	4	6	2	1	83	6	3	50	2	1
25	2330	1.012	"	"	"	0.2740	16.47	0.5719	0.8459	65	18	1	10	4	1	80	12	10	0	0	0
26	1000	1.027	"	"	"	0.6394	20.0	0.1830	0.7714	100	10	4	23	3	2	95	14	8	0	0	0
27	1899	1.018	"	Trace	"	0.7851	10.46	....	....	...	...	...	...	...	...	...	...	...	...	...	...
28	3210	1.022	Neutral	None	Present	0.9707	40.12	0.7887	1.7594	80	8	7	80	2	1	82	9	7	0	0	0
29	715	1.016	Acid	"	None	0.8482	10.01	0.1248	0.4780	75	4	5	55	4	2	100	15	4	50	3	1
30	1080	1.023	"	"	"	0.7020	20.08	0.1923	0.9548	60	10	2	30	3	3	100	8	3	100	2	1
31	1110	1.020	"	"	"	0.4662	19.42	0.3193	0.7855	100	9	6	32	6	½	100	9	2	100	2	0.5
32	1865	1.016	"	"	"	1.054	21.84	0.0997	1.1637	78	6	2	20	5	2	86	12	10	100	3	1
33	680	1.010	"	"	"	0.1909	3.06	0.1165	0.3164	63	15	4	76	3	2	90	7	5	50	2	1
34	420	1.022	"	"	"	0.3457	9.24	0.2127	0.5584	100	10	5	5	4	1	100	9	6	0	0	0
35	1140	1.020	"	Trace	"	1.52	14.82	....	....	...	...	...	...	...	...	...	...	...	...	...	...
36	1020	1.015	"	None	"	0.5829	15.31	0.0300	0.6120	100	8	3	30	3	2	100	5	2	100	2	1

37	680	1.021	Acid	Trace	None	0.6785	15.64	0.4327	1.1112	100	7	1	25	0	1	80	8	3	50	4	1
38	975	1.022	"	None	"	0.7527	19.01	....	....	...	...	...	...	...	...	...	...	...	...	...	...
39	1830	1.015	"	"	"	0.8044	16.62	0.5568	1.3095	100	10	6	16	1	1	100	15	6	50	8	1
40	1670	1.013	"	"	"	0.8416	16.7	0.2094	1.0510	80	14	2	21	8	2	85	10	4	0	0	0
41	2470	1.006	"	"	"	1.0178	13.58	....	....	...	...	...	...	...	...	...	...	...	...	...	...
42	710	1.027	"	"	"	0.5602	17.04	0.892	0.9522	75	4	1	54	2	½	65	8	4	0	0	0
43	1640	1.012	"	"	"	0.9043	17.22	....	....	82	12	6	32	5	½	100	12	7	100	2	1
44	1165	1.021	"	"	"	1.1545	22.72	....	....	100	8	4	27	4	2	100	12	5	100	2	1
45	2020	1.012	"	"	"	2.23	28.28	....	....	60	10	8	50	7	2	80	7	4	100	8	½
46	1000	1.010	"	"	"	0.3102	5.0	0.07	0.3829	62	6	2	52	4	1	65	15	10	50	2	1
47	4160	......	"	Trace	235.0	0.4892	45.70	1.1598	1.6490	100	7	4	80	3	½	80	8	4	50	2	½
48	930	1.016	"	"	None	0.5653	20.59	0.5783	1.1436	80	16	8	6	8	2	75	8	8	50	8	½
49	760	1.027	"	None	"	2.2784	26.6	....	....	100	13	2	12	4	1	100	10	3	50	3	1
50	955	1.015	"	Trace	"	0.6060	15.6	0.2521	0.8581	75	4	2	50	5	2	100	9	0	50	2	1

a has reference to the percentage number showing granules; *b* indicates the maximum, and *c* the average number of granules in each leucocyte.

TABLE II.

No.	Diagnosis.	Urea.	Uric acid.	Uric-acid coefficient.	Xanthin bases.	Alloxuric bodies.	Alloxuric coefficient.	No.	Diagnosis.	Urea.	Uric acid.	Uric-acid coefficient.	Xanthin bases.	Alloxuric bodies.	Allox-uric coefficient.
1	Arterio-sclerosis	15.6	0.6060	1 : 25.7	0.2521	0.8581	1 : 18.1	14	Uric-acid diathesis	15.64	0.6785	1 : 11.6	0.4327	1.1112	1 : 14.0
2	Chronic gout	12.0	0.66	1 : 18.6	0.044	0.704	1 : 17.0	15	Migraine	16.7	0.8416	1 : 20.8	0.2094	1.0510	1 : 15.8
3	Chronic gout	11.2	0.1817	1 : 61.6	0.383	0.5647	1 : 19.7	16	Uric-acid diathesis	17.04	0.5602	1 : 30.4	0.392	0.9522	1 : 17.8
4	Uric-acid diathesis	21.5	0.2336	1 : 92.0	1.0791	1.3127	1 : 16.1	17	Chronic gout	17.22	0.9043	1 : 17.8			
5	Chronic gout	18.48	1.1523	1 : 16.0	0.0884	1.2407	1 : 14.8	18	Uric-acid diathesis	22.72	1.1545	1 : 19.6			
6	Chronic gout	15.99	0.5166	1 : 30.9	0.7083	1.2219	1 : 13.0	19	Migraine	19.42	0.4662	1 : 41.6	1.002	1.4682	1 : 15.2
7	Uric-acid diathesis	24.16	1.9787	1 : 12.2				20	Uric-acid diathesis	19.01	0.7527	1 : 25.2	0.2916	1.0478	1 : 18.1
8	Lithiasis	17.88	0.7384	1 : 24.2	0.2035	0.9419	1 : 18.9	21	Uric-acid diathesis	13.58	1.6178	1 : 8.3			
9	Migraine	20.0	0.6384	1 : 31.0	0.1330	0.7714	1 : 25.9	22	Lithiasis	5.0	0.3192	1 : 15.6	0.07	0.3892	1 : 12.8
10	Chronic gout	10.46	0.7851	1 : 13.3				23	Uric-acid diathesis	19.38	0.2785	1 : 69.5	0.4306	0.7091	1 : 27.3
11	Chronic gout	21.84	1.054	1 : 20.7	0.9897	1.1537	1 : 18.0	24	Lithiasis	20.59	0.5653	1 : 36.4	0.5783	1.1436	1 : 18.0
12	Migraine	3.06	0.1999	1 : 15.3	0.1165	0.3164	1 : 9.6	25	Uric-acid diathesis	26.6	2.2784	1 : 11.7			
13	Lithiasis	14.82	1.52	1 : 9.7											

CASE 1.—A. J., female, aged sixty-four years. Family history of rheumatism and gout. Seven years ago was paralyzed on right side. Arterio-sclerosis well marked. A great deal of mental depression.

CASE 2.—E. S., female, aged seventy-eight years. Gouty family history. Arterio-sclerosis.

CASE 3.—C. W. C., male, aged fifty-six years. Gouty family history. A great sufferer from gout for many years. Tophi. Arterio-sclerosis.

CASE 4.—E. O., male, aged thirty years. Gouty family history. Some uric-acid symptoms. Otherwise normal.

CASE 5.—M. B. W., female, aged sixty-eight years. Rheumatism and insanity in family. Pronounced neurasthenia. Arterio-sclerosis. Epithelioma of neck. Marked anæmia.

CASE 6.—E. M. S., male, aged forty-two years. Family history of gout. Chronic neurasthenia. Arterio-sclerosis.

CASE 7.—J. M. G., male, aged forty years. Marked history of chronic Bright's disease on both sides of family. Influenza.

CASE 8.—D. C., male, aged sixty-five years. Nothing in family history. Well-marked arterio-sclerosis. Typical uric-acid diathesis. Neurasthenia.

CASE 9.—J. W. S., female, aged forty-six years. Father died of heart disease. Climacteric hysteria.

CASE 10.—F. L., female, aged fifty-two years. Marked family history of gout. Chronic gout and neurasthenia. Lithiasis.

CASE 11.—M. W., female, aged twenty-three years. History of gout and Bright's disease on mother's side. Father has calculous pyelitis. Chlorosis and typhoid fever, second week; temperature 101° to 103° F.

CASE 12.—J. C. H., male, aged thirty-five years. Neurasthenia.

CASE 13.—V. E. E., female, aged sixty-five years. Rheumatism in family. Formerly suffered a great deal with migraine. Neurasthenia. Chronic gout. Tophi. Arterio-sclerosis.

CASE 14.—P. C., male, aged twenty-five years. Marked gouty history. Neurasthenia. Uric-acid diathesis.

CASE 15.—W. M. L., male, aged forty years. Septic infection.

CASE 16.—S. P. L., male, aged twenty-three years. Rheumatic family history. Lithiasis (?).

CASE 17.—L. S., female, aged thirty-two years. Nothing in family history. Mild chlorosis.

CASE 18.—F. L., male, aged forty-two years. Rheumatism and gout in family. Chronic Bright's disease, following acute nephritis.

CASE 19.—M. H., male, aged (?). Amputation of foot for railroad accident.

CASE 20.—T. H., male, aged fifty-eight years. Gouty ancestry. Arterio-sclerosis. Uric-acid diathesis. Neurasthenia.

CASE 21.—Miss P., aged about forty years. Uric-acid diathesis. Chronic neurasthenia.

CASE 22.—Mrs. B., aged sixty-six years. Father died of heart disease; mother suffered with migraine. Had migraine as a young woman. Myoma of the uterus. Four years ago was operated upon for carcinoma of the left breast. Local recurrence two months ago. Diabetes developed two years after operation. Marked obesity.

CASE 23.—Male, aged fifty years. Nothing in family history. Typical lithiasis and myelitis. For many years migraine.

Case 24.—C. L. D., male, aged thirty-one years. Some rheumatism in family. Neurasthenia.

Case 25.—C. E., male, aged twenty-six years. Neurasthenia.

Case 26.—G. F. G., male, aged thirty-one years. Migraine on both father's and mother's side. Migraine during the last four years.

Case 27.—Miss McC., aged about forty years. Gouty family history. Hysteria. Tophi.

Case 28.—M. T., female, aged fifty-one years. Rheumatism and gout in family. Diabetes. Arterio-sclerosis. Tophi.

Case 29.—C. N., female, aged thirty-six years. Father died of nephritis. Migraine since childhood. Severe neurasthenia. Weight, seventy-four pounds.

Case 30.—J. M. F., male, aged thirty-six years. Uric-acid diathesis. Neurasthenia.

Case 31.—E. B., female, aged twenty-seven years. Very marked family history of migraine. Migraine since fifteen years of age. Neurasthenia.

Case 32.—Mrs. C., aged fifty-six years. Migraine in family. Migraine since childhood. Arterio-sclerosis.

Case 33.—W. L. T., female, aged forty-five years. Migraine on both sides of family. Migraine since childhood. Beginning climacteric.

Case 34.—Mrs. B., aged twenty-six years. Chlorosis and neurasthenia.

Case 35.—Mrs. H., aged forty years. History of nephritis and lithiasis. Chronic gout. Tophi. Nephrolithiasis.

Case 36.—Miss P., aged thirty years. Rheumatism in family. Neurasthenia.

Case 37.—E. B. B., male, aged forty-seven years. Nothing in family history. Rheumatism at seventeen years of age. Marked uric-acid diathesis. Much mental depression.

Case 38.—Mr. P., aged about fifty years. Uric-acid diathesis. Neurasthenia.

Case 39.—A. P., male, aged thirty-two years. Neurotic family history. Pseudo-leucæmia.

Case 40.—T. N. C., male, aged about thirty-eight years. Migraine in the family. Migraine since childhood. Some arterio-sclerosis.

Case 41.—S. E. C., male, aged thirty-two years. Neurotic family history. Neurasthenia. Uric-acid diathesis.

Case 42.—S. J. L., male, aged fifty-four years. Some rheumatism (gout?) in family. Nephrolithiasis.

Case 43.—Mrs. G., aged about forty years. Nothing in family history. Chronic gout. Tophi.

Case 44.—J. T. F., male, aged about fifty years. Nothing in family history. Uric-acid diathesis. Neurasthenia.

Case 45.—M. F., female, aged thirty-eight years. Neurotic family history. Neurasthenia.

Case 46.—J. A. L., male, aged sixty-three years. One brother died of heart disease. Nephroliathisasis. Arterial sclerosis. Heart disease.

Case 47.—Mrs. T., aged about fifty-eight years. Rheumatism in family. Diabetes. Chronic gout.

Case 48.—Mr. B., aged about fifty years. Migraine in family. Nephroliathiasis.

Case 49.—Miss C., aged forty-two years. Chronic gout. Gouty ancestry. Marked neurasthenia.

CASE 50.—H. J., female, aged sixty years. Nothing special in family. Uric-acid diathesis. Arterio-sclerosis.

From an analysis of these cases it is at once apparent that a constant relation between the presence of the granules and the elimination of uric acid or xanthin-bases does not exist. For, while in a number of instances the granules were present in large numbers, coincidently with an increased elimination of uric acid or of the xanthin-bases, or both, there were others in which but few granules occurred with an increased elimination, or many granules with a diminished elimination, of the alloxuric bodies in the urine.

My personal observations on the occurrence of Neusser's granules in the blood are thus entirely in accord with those of Futcher, and in no way bear out the claims of Neusser and Kolisch.

Experiments undertaken with a view of reconciling the difference in the results reached by different observers have thus far been unsuccessful. Whether or not Ehrlich's view,[1] who regards Neusser's granules as artefacts, and states that they are only rarely observed when strictly pure solutions made up from the crystalline dyes are used, be correct, I am not prepared to say, but am rather inclined to doubt.

In the study of the final question, which suggested itself for investigation—*i. e.*, to what extent an increased elimination of uric acid, as such, and of the alloxuric bodies as a whole, plays a part in the symptomatology of the uric acid diathesis—some difficulty was experienced in the selection of the proper subjects. This was owing to the absence of a proper definition of just what is meant by the uric-acid diathesis. Gout and liathiasis, experience has shown to be associated in some manner with an abnormal metabolism, as the result of which some of the uric acid formed within the body, or introduced from without, is retained and deposited in the joints, along the tendons, in the pelvis of the kidney and the like, where it may or may not give rise to clinical symptoms. Such cases, of course, were directly accepted. But aside from these cases there are others in which no symptoms referable to local irritation are found, but in which, associated with certain nervous and digestive symptoms, such as depression of spirits, feelings of apprehension, moodiness, irritability, a want of self-reliance, and various subjective dyspeptic manifestations, we find a scanty, high-colored urine which, upon standing, deposits an abundant sediment of uric-acid crystals. This condition constitutes what is generally spoken of as lithæmia, or uric-acid diathesis in the more limited application of the term. Such cases were, hence, likewise included, as were also those of migraine and arterio-sclerosis in which distinct improvement followed a treatment directed toward an increased elimination and diminished ingestion of uric acid and its congeners. Other conditions, which by some have also been ascribed to a uric-acid diathesis, such as muscular rheumatism, diabetes, leucæmia, etc., were excluded from investigation, as sufficient evidence has not as yet been advanced to warrant the conclusion of a causal connection existing between these diseases and the diathesis in question. The results obtained are given in Table II.

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[1] Ehrlich and Lazarus. Die Anæmie. I. Abtheilung. Wien. A. Hoelder, 1898, p. 28.

Upon studying this table, it will be seen that an absolute increase in the elimination of uric acid is only occasionally observed, viz., in cases 5, 7, 11, 13, 14, and 18, while an increase in the coefficient *uric acid: urea*, is obtained in almost all cases. An increase in the amount of alloxuric bodies, on the other hand, is likewise not constantly met with, but it will be observed that in some cases in which a normal amount of uric acid and a normal uric-acid coefficient are encountered the alloxuric bodies as a whole may be considerably increased. This is notably the case in No. 4, in which only 0.2336 grm. of uric acid with a coefficient of 1 : 92.0 was found, while the alloxuric bodies conjointly amounted to 1.3127. The alloxuric acid coefficient, however, was found increased in all cases, so that we are forced to the conclusion that, while the uric acid occurs in relatively increased amount in the great majority of cases of the uric-acid diathesis, the alloxuric coefficient is in reality the deciding factor, and plays an important rôle in the symptomatology of this condition.

From these observations, however, it would be erroneous to conclude that we are dealing with a uratic subject whenever the alloxuric coefficient is increased, as this may occur in a great variety of diseases, which unquestionably are in no wise dependent upon such an increase. Now, as before, then, the diagnosis of the uric-uric diathesis will have to be based not only upon the finding in the clinical laboratory, but upon the subjective symptoms and physical signs as well. Whether or not cases of the diathesis ever occur in which such an increase is not observed I am not prepared to decide from personal observations, but admit that it is quite possible.

In conclusion I wish to insist upon the necessity of a quantitative estimation in the diagnosis of the uric-acid diathesis, and that not too much reliance be placed upon a simple macroscopical or microscopical examination of the urine. At times, of course, this may be sufficient, when very heavy sediments occur, but more commonly the greater portion of the uric acid is held in solution, and would escape detection altogether, unless a direct quantitative examination were made.